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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/849,400	05/07/2001	Ai J. Lin	P66823US0(WRAIR-01)	9445

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Office of the Staff Judge Advocate
U.S. Army Medical Research and Materiel Command
ATTN: MCMR-JA (Ms. Elizabeth Arwine)
504 Scott Street
Fort Detrick, MD 21702-5012

EXAMINER	
PATEL, SUDHAKER B	
ART UNIT	**PAPER NUMBER**
1624	15

DATE MAILED: 10/22/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/849,400	Al J. Lin et al
Examiner	**Art Unit**
Sudhaker Patel	1624

-- The MAILING DATE of this communication appears on the cover she t with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on Aug 26, 2002

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 1-31 is/are pending in the applica

4a) Of the above, claim(s) 4, 8, 9, and 13 is/are withdrawn from considera

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 1-3, 5-7, 10-12, and 14-31 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☒ Claims 1-31 are subject to restriction and/or election requirem

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 6,8,9
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicants' communication paper # 14 dated 8/26/02 is acknowledged.

(I). Restriction/Election: Applicant's election without traverse of invention of Group III, Claims(in part) 1-3,5-7, 10-12, 14-31 drawn to compounds, a simple composition, and the first recited method of use of generic Formula of claim 1 wherein X = S i.e. tricyclic phenothiazine core, together with the species wherein Y = pyrrolidinyl with integer n = 4 in the above mentioned Paper No. 14 is also acknowledged. Claims 4,8,9,13 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. Accordingly, this application will be examined bearing in mind the subject matter of invention of Group III as elected by the applicants only. Applicants are urged to correct the claims and their dependency in reply to this Office Action.

The restriction/election is considered proper, and is made **FINAL.**

(II). ***Information Disclosure Statement***

1. The information disclosure statements paper # 4,6,7,8,10 filed on 8/14/01, 11/2/01, 11/28/01, and 3/8/02 respectively fail to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because certain copies of the cited references have not been provided. It has been placed in the application file, but the missing information referred to therein has not been considered as to the merits. Applicants are advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any

missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609 C(1).

Copies of above mentioned papers are enclosed herewith for applicants' records.

(III). ***Claim Rejections - 35 U.S.C. § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3,5-7, 10-12, 14-31 are rejected under 35 U.S.C. 112, paragraph second, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. The following reasons apply:

(A). In claim 1, variable X is defined as: " substituted or unsubstituted alkyl or a heteroatom". It is not very clear as to what applicants wish to recite. It is confusing to read X as alkyl because it can be any chain length which will affect the ring size and/or side. "Alkyl" represents a monovalent group(as defined in specification at page 10, lines 18-20) and therefore it is confusing how the ring/ chain member which is a bivalent moiety can be "Alkyl".

(B). It is also not very clear as to "heteroatom" which is recited for X, R1, R2 which is not defined in the specification. The only definition provided is "S". Claim 2 defines heteroatom as S only. Typically a "heteroatom" is any "non-carbon" atom. Accordingly, the metes and bounds are

unclear, because it could include N, O, Halogen, P, Si etc. Specifications also remains silent(see page 7 lines 4-5, line 7) for X. Specification on page 3 line 27 defines X = S , which is the only heteroatom other than carbon atom defined. Accordingly, correction is required.

(C). In claim 1 line 13, Y is recited to represent it as: " N(10R1)(R2)". Necessary correction is required.

(D). Claims 2, 11 recite X = C ,S or ethyl. The valencies of Carbon atom are not satisfies when X = C. Also, it is not ver clear as to X = ethyl which is C2H5 group. Therefore, it is confusing to read the exact definition of X component.

(E). Claims 5,6 only recite "intended use" and do not further limit scope of claim 1. See MPEP 2106:

The subject matter of a properly construed claim is defined by the terms that limit its scope. It is this subject matter that must be examined. As a general matter, the grammar and intended meaning of terms used in a claim will dictate whether the language limits the claim scope. Language that suggests or makes optional but does not require steps to be performed or does not limit a claim to a particular structure does not limit the scope of a claim or claim limitation. The following are examples of language that may raise a question as to the limiting effect of the language in a claim:

(A) statements of intended use or field of use,

(B) "adapted to" or "adapted for" clauses,

© "wherein" clauses, or

(D) "whereby" clauses.

The "intended use" in the instant claims does not result in a structural difference (see MPEP 2111.02:

During examination, statements in the preamble reciting the purpose or intended use of the claimed invention must be evaluated to determine whether the recited purpose or intended use results in a structural difference (or, in the case of process claims, manipulative difference) between the claimed invention and the prior art. If so, the recitation serves to limit the claim. See, e.g., In re Otto, 312 F.2d 937, 938, 136 USPQ 458, 459 (CCPA 1963) (The claims were directed to a core member for hair curlers and a process of making a core member for hair curlers. Court held that the intended use of hair curling was of no significance to the structure and process of making.); In re Sinex, 309 F.2d 488, 492, 135 USPQ 302, 305 (CCPA 1962) (statement of intended use in an apparatus claim did not distinguish over the prior art apparatus). If a prior art structure is capable of performing the intended use as recited in the preamble, then it meets the claim. See, e.g., In re Schreiber, 128 F.3d 1473, 1477, 44 USPQ2d 1429, 1431 (Fed. Cir. 1997) (anticipation rejection affirmed based on Board's factual finding that the reference dispenser (a spout disclosed as useful for purposes such as dispensing oil from an oil can) would be capable of dispensing popcorn in the manner set forth in appellant's claim 1 (a dispensing top for dispensing popcorn in a specified manner)) and cases cited therein. See also MPEP § 2112 - § 2112.02.

(F). Claim 5 recites the functions of compound of claim 1 as:" modulates, attenuates, reverses, affects, or combination thereof". It is confusing to visualize these functions. The mode of action for combination would be other than the simple single function. Clarification is requested.

(G). Claim 5 recites " a cell's or organism's resistance". It is not very clear as to what is included by a cell and organism. Clarification is required.

(H). Claim 5 recites compounds of claim 1 and also "given drug or compound". It is not very clear as to the definition of compound as recited in claim 6. Are compounds of claim 1 antimalarials?

(I). Claims 7, 9 are related to compounds of claim 1. Claim 7 which is dependent of claim 1, recites compounds which are not having phenothiazine core(see lines 17-33). It is not exactly clear as to what applicants want to say.

Claim 9 recites exclusion of majority of compounds of claim 7. If this is done to avoid prior art(s), applicants are urged to disclose and provide copies of the same and their relevancy to instant claim(s), as it would be necessary for the examination of the same.

(J). Claim 30 recites " a method of ....., preventing or inhibiting malaria in a subject comprising administering to the subject..." which is indefinite because prevention and inhibition are different processes. Also, the process or step of "administering" is not exactly defined. Clarification is required.

(K). Claims 31 recites"antimalarial" which is not definite. It is not defined in any of the previously cited claims. Specification also remains silent.

IV. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3,5-7, 10-12, 14-31 are rejected under 35 U.S.C. 112, para one because the specification, while enabling as a method of using the compounds for treatment, does not reasonably provide enablement for method of "preventing or inhibiting malaria" by a function: " modulating, attenuating, reversing, affecting, or combination thereof , a cell's or organism's resistance". Most of the compounds have N-substituted phenothiazine core common whereas the claim language include many compounds as represented by variables n and Y in the generic claim 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are drawn to compounds, compositions, prodrugs, and method(s)(but not limited to) of prevention or treatment or inhibition of malaria in a generic subject.

In evaluating the enablement question, several factors are to be considered. In re Wands, 8 USPQ 2d 1400 (Fed. Cir. 1988); Ex parte Forman, 230 USPQ 546. The factors include:***(1).*** The nature of invention;***(2).*** the state of prior art ;***(3).*** the predictability or lack thereof in the art; ***(4).*** the amount of direction or guidance present;***(5).*** the presence or absence of working examples;***(6).*** the breadth of the claims, and ***(7).*** the quantity of experimentation needed.

1). Significance of in vitro and in vivo studies:

In this respect Wongsrichanalai et al (PubMed Abstr.:11937421; Lancet Infect Dis 2002 Apr;2/4:209-18) states that " Chloroquine resistance spread across Africa during the 1980s, and severe resistance is especially found in East Africa. As a result, more than ten African countries have switched their first-line drug to sulfadoxine-pyrimethamine. Of great concern is the fact that the efficacy of this drug in Africa is progressively deteriorating, especially in foci in east Africa, which are classified as emerging MDR areas. Urgent efforts are needed to lengthen the life span of..... and to identify effective affordable, alternative antimalarial regiments..... Polymorphism in pfmdr1 may also be associated with resistance to chloroquine, mefloquine, quinine, and artemisinin. Use of such genetic information for the early detection of resistance foci and future monitoring of drug-resistant malaria is a potentially useful epidemiological tool, in conjunction with the conventional in vivo and in vitro drug-sensitivity assessment".

2).Chloroquine and other alternatives:

Rahman et al (PubMed Abstr.:11816441;Trans R. Soc Trop Med Hyg 2001 Nov-Dec;95/6:661-7) states that " There were significantly more clinical and parasitological failures with chloroquine than with Q3 + SP (= quinine sulfate + Sulfadoxine-pyrimethamine, which we now recommend as a better (but far from ideal) choices for first line therapy..... Further studies are needed to determine the optimum treatment for malaria in Bangladesh".

3).Other antimalarials in pregnancy:

McGready et al (PubMed:11712093; Clin Infect Dis 2001 Dec 15;33/12;2009-16) states that "The emergence and spread of MDR Plasmodium falciparum compromises the treatment of

malaria, especially during pregnancy, where the choices of antimalarials is already limited. The artemisinins were tolerated..... These results are reassuring, but further information about safety of these valuable antimalarials in pregnancy is needed".

(4).Severe acute renal failure(ARF) in malaria:

Mehta et al (PubMed:11590286; J. Postgrad Med 2001 Jan-Mar;47/1;24-6) concludes that ARF necessitating dialysis was seen in 92% of patients with ARF in malaria. Plasmodium falciparum infection, severe ARF, ... were poor prognostic factors. Resistance was noted to both chloroquine and artesunate".

Specification on pages 28-34 describes the in vitro assay methods used for the activity of the claimed compounds and recited as:

Table 2 of page 30 showing comparison against Chloroquine and mefloquine.

Table 3 of page 32 showing Fractional inhibitory concentration in 1:1 combination of drug and chloroquine with Verapamil only as a reference.

There is no demonstration for the ability to prevent or inhibit malaria in a generic subject" as claimed herein by "a process or step of administering to a subject a therapeutically effective amount of a compound or its pharmaceutically acceptable salt or a prodrug thereof of generic Formula of claim 1 for various generic cell's or organism's resistance to a given generic drug as antimalarial.

Therefore, the state of the art as mentioned earlier, provides the need of undue experimentation for the instantly claimed therapeutic benefits for a subject involving gender(s)

and various body parts. The facts provided as above do support the need for additional quantity of experimentation which would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the method of preventing or inhibiting malaria as recited herein.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the use as a method of preventing or inhibiting malaria as claimed herein.

V. *Claim Rejections - 35 U.S.C. § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-3,5-7, 10-12, 14-29 (readable on Formula of claim 1 wherein X = S i.e phenothiazine core, are rejected under 35 U.S.C. 102(b) as being anticipated by Foldeak et al(Chem.Abstr./CAS Abs. # 123:313990-1995:916427; also cited as Hung. Teljes, 299 pp as HU 66860 dated 1/30/1995). See Formula I wherein X = H; R1 and R2 = H, C1-6 alkyl or -NR1R2 forming 5-7 membered saturated. Or unsaturated heterocyclic rings, and may contain other heteroatoms; alk = **C2-C6 linear** or branched alkylene.The instantly claimed compounds read on the compounds of the reference.

VI. ***Claim Rejections - 35 U.S.C. § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3,5-7, 10-12, 14-29 (readable on Formula of claim 1 wherein X = S i.e phenothiazine core, are rejected under 35 U.S.C. 103(a) as being unpatentable over Foldeak et al(Chem.Abstr. 123:313990; also cited as Hung. Teljes, 299 pp as HU 66860 dated 1/30/1995). See Formula I wherein X = H; R1 and R2 = H, C1-6 alkyl or -NR1R2 forming 5-7 membered saturated Or unsaturated heterocyclic rings, and may contain other heteroatoms; alk = C2-C6 linear or branched alkylene and further in view of Halt et al(EP 361485).

The applicants claim generically N substituted phenothiazine derivatives of Formula of claim 1 wherein X = S, Y = Pyrrolidine, n = 4. Applicants further claim the use of compounds, their compositions, and prodrugs as antimalarials and MDR agents.

Foldeak teaches making of substituted Phenothiazine and pharmaceutical compositions as antiplasmid.

The reference '860 differs from the instant compounds by also having **substituent X = other than H i.e. halogen or trialkylsilyl** in the molecule.

The other reference '485 teaches making of compounds and method of sensitizing multidrug resistant (MDR) cells using phenothiazines(PTZs) and thioxanthenes. See compounds of Formulae of Table 1 on page 13, and compounds (wherein R = Nitrogen containing saturated rings) of Formulae of Table 2 on page 15; for compounds (wherein R = -(CH2) 2-4 -N-dialkyl)of Formulae of Table 3 on page 16. In addition to making of compounds, Halt also teaches the effect of side chain amino group in the use of compounds for inhibition of cell growth and MDR(see Table 5 on page 20).

The instant compounds differ from the ref. '485 by having values for integer n = 4-6, and R1, R2 are each independently a heteroatom, cycloalkyl, aryl or heteroaryl, in addition to H, and (substituted or unsubstituted) alkyl.

One of ordinary skill in the art would have been motivated to select the claimed compounds from the reference Foldeak genus and modify the core of ref.'485 since such compounds would have been suggested by the reference as a whole. However, it would have been obvious to a chemist skilled in the art to select any species of the genus Foldeak and change/replace -alk-NR1R2- bridge similar to ref.'485 that will have reasonably similar properties and expect equal or better pharmaceutical use as MDR agents. One of ordinary skill in the art would have been motivated to make the claimed compounds by combining and or exchanging the bridges of the references since such compounds would have been suggested by the reference as a whole. The requisite motivation stems from the expectation that compounds so

structurally similar would be expected to possess pharmaceutical properties(in re Wood, 199 USPQ 137).

Therefore, the reference '485 clearly teaches the MDR activity of derivatives of phenothiazine compounds, their relationship with in vitro testing activity, thereby providing motivation to one of ordinary skill in the art to prepare the modified compounds of genus of ref. Foldeak and expect improved or a better method of sensitizing multidrug resistant cells to antimalarial agents as claimed herein.

Claims 1-3,5-7, 10-12, 14-29 (readable on Formula of claim 1 wherein X = S i.e phenothiazine core, are also rejected under 35 U.S.C. 103(a) as being unpatentable over Uffe Bang Olsen(U.S.P. 5741791).

Olsen teaches making of substituted phenothiazine as claimed herein. See Formula of abstract, compounds included by Formula I of specification in column 2 lines 10-67, and compounds as recited in claim 1 in column 25 lines 25-59, wherein X = S, Y = N, R4/R5 = H, integer r = 1-3, m = 1, n = 0, R6 = OH or C_{1-8} alkoxy. This will make compounds with N-$(CH2)_{1-3}$--Pyrrolidine substituted with -COOH or -CO-alkyl.

Olsen differs from the instant compounds by having one -CH2- group less i.e. instantly claimed compounds have a minimum of -(CH2)4-.

One of ordinary skill in the art would have been motivated to select the claimed compounds from the reference Olsen genus and modify the core either alone or in combination

with the prior art ref.'485 or Foldeak et al, since such compounds would have been suggested by the references as a whole.

While applicants claim their compounds to be novel, they are not non-obvious over the cited prior art(s). It can not be ignored that prior art(s) compounds as recited earlier and above are involving the concept of adjacent homologies consisting of -CH2- group. There are ample of cases recited with such homologies. Applicants' compounds are forming higher homologue(s) than the ref. Compounds(in that instant compounds having -(CH2)4 instead of -(CH2)3-, and such homologies are not deemed patentably distinct absent evidence of superior, unexpected results. Note Ex parte Ruddy 121 USPQ 427: Ex parte Nathan 121 USPQ 349; In Shetty 195 USPQ 753 regarding patentability of homologies. For adding or removing one or two methyl groups on a carbon atom where none existed before, to extend the length of an alkyl chain. In re Grosse, 201 USPQ 57,63,(" The known structural relationship between adjacent homologue, for example, supplies a chemical theory upon which a prima facie case of obviousness of a compound may rest").

It has been held that a prior art disclosed compounds is sufficient to render a prima facie case of obviousness as species falling within a genus. See In re SUSI, 440 F 2d 442, 169 USPQ 423, 425 (CCPA 1971), followed by Federal Circuit in Merck & co. V. Biocraft Laboratories, 847 F 2d 804, 10 USPQ 2d 1843, 1846 (Fed. Cir.1989).See In re Dillon 16 USPQ 2nd. 1897, 1923 regarding a prima facie case of obvious ness of structurally similar compounds disclosed by prior art regardless of the properties disclosed in the inventor's application.

All this is especially considered so in the absence of timely, verified, comparative data, commensurate in scope to the claims sought, clearly and convincingly proving obvious ness over the art(s) as applied above. If applicants intend to rely on unusual or unforseen results demonstrate patentability, attention is drawn to MPEP 716. It is also pointed out that arguments of patentability to differences either not in, or not made clear by, claim language will be of no avail as it is the claims, per se, that are the measure of the invention.

This application has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicants' cooperation is, therefore, requested in promptly correcting any errors of which they may become aware in the specification.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sudhaker Patel,D.Sc.Tech. whose telephone number is (703) 308 4709.

The examiner can normally be reached on Monday thru' Friday from 8:30 AM to 5:00 PM. If attempts to reach the examiner by the phone are unsuccessful, the examiner's supervisor, Dr.Mukund Shah can be reached at (703) 308 4716 or Sr. Examiner Mr. Richard Raymond at (703) 308 4523.

A facsimile center has been established for Group 1600. The hours of operation are Monday through Friday, 8:45 AM to 4:45 PM. The telecopier numbers for accessing the facsimile machine are (703) 308-4556 or (703) 305-3592.

Any inquiry of general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308 1235.

RICHARD L. RAYMOND
PRIMARY EXAMINER
ART UNIT 1624

Sp/October 21, 2002.